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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/885,894	06/20/2001	Gregory S. Shelness	9151.18	4865

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EXAMINER	
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ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/885,894	SHELNESS, GREGORY S.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *93-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/8/02, 6/9/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1 (original claims 1-22 and currently presented as claims 93-114) in the reply filed on 11/2/2007 is acknowledged. The traversal is on the ground(s) that a search of original Group I would overlap with a search of Group II, and therefore the Groups I and II should be examined together. This is not found persuasive because Groups I and II are drawn to lipophilic and amphipathic compounds, respectively, and therefore are drawn to compounds which are structurally different and have different chemical/physical properties, and as such constitute separate inventions.

The requirement is still deemed proper and is therefore made FINAL.

2. Applicant's election, without traverse, of the following species is noted:

Antibody (as the heterologous moiety species)
ApoB 19.5 (as the truncated ApoB protein species)
Phosphatidylcholine (as the polar lipid species)
Triglyceride (as the neutral lipid species)
Small emulsion particle (as the particle species)

3. In the responses received on 10/24/2002 and 11/2/2007, the Applicant cancelled claims 1-38 and 39-92, respectively. Applicants have added new claims 93-114, which are currently pending and the subject of this office action.

Information Disclosure Statement

1. The information disclosure statement received on 10/8/2002 has been considered. Citation #4 has not been considered. US 6,177,544 is not Woo et al, as indicated on the IDS, but rather is Kanai et al, drawn to a collage-based auxilary agent for opthalmic surgery.

2. The information disclosure statement received on 6/9/2003 has been considered.

Claim Objections

1. The Examiner suggests amendment of claims 93(d) and 113(d) to recite "0.5" rather than ".5". Furthermore, it is suggested to amend claim 93(d) to recite "wherein the LDL receptor binding region is deleted in said truncated apoplipoprotein B", or something similar. As written, the claim can be interpreted as an truncated apolipoprotein B protein lacking the LDL receptor binding region, or alternatively, a particle having a deleted LDL receptor binding region.

2. Claim 101 is objected to for failing to recite a lower limit for the claimed range of ApoB molecules. Furthermore, with the election of ApoB 19.5, the recitation of other ApoB molecules represents a recitation of non-elected subject matter.

3. Claims 106-107 are objected to for recitation of non-elected subject matter. With the election of phosphatidylcholine and triglyceride, the recitation of other polar and neutral lipid species represents non-elected subject matter.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breath of claims. Ex Parte Forman, (230 USPQ 546 (Bd. Pat. App. & Int. 1986); In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Claims 93-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a lipoprotein compound delivery particle comprising a truncated apolipoprotein B

(ApoB) protein that is ApoB 17, wherein said ApoB is fused to a single chain anti-Her2 antibody, does not reasonably provide enablement for a lipoprotein compound delivery particle comprising any other truncated ApoB protein comprising any other fused heterologous moiety. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to a lipoprotein compound delivery particle comprising a truncated ApoB protein. The specification, on page 13, lists numerous truncated ApoB molecules, and states that ApoB fragments ranging in size from ApoB 6 to ApoB 74 can comprise the claimed lipoprotein compound delivery particle. However, the breadth of independent claim 93 is excessive in that is reads on any truncated ApoB protein without a LDL receptor binding region. Given the broadest reasonable interpretation, the claim reads on the ApoB fragments recited in the specification, but also on fragments having less than 270 amino acids, or even 1-2 amino acid fragments of ApoB. The specification does not provide guidance or examples showing how to make and then use lipoprotein compound delivery particles using such small ApoB fragments. Furthermore, the specification provides guidance and examples showing one ApoB fragment, ApoB 17, that is capable of sequestering lipid in the form of discoidal lipoprotein particles, wherein said particles are capable of delivering a pharmaceutical agent.

The claims are further drawn to the claimed particles, wherein said truncated ApoB protein further comprises a fused heterologous moiety, wherein said heterologous moiety is a member of a specific binding pair. There is no guidance or examples showing that any ApoB protein, other than ApoB 17, can be fused to any other heterologous moiety other than a single chain anti-HER2 antibody, and still retain biological activity of both the ApoB fragment and the heterologous moiety. One of ordinary skill in the art would know that the physical comformation and/or protein folding of one pair of peptide fragments would likely differ from that of another peptide pair, and therefore a skilled artisan would not be able to predict the effect on protein conformation and/or physico/chemical properties of ApoB fragments other than ApoB 17 fused to any other heterologous moiety other than single chain antibodies, such as single chain anti-HER2 antibodies.

For these reasons, which include the breadth of the claims with regards to all possible truncated ApoB proteins and all possible heterologous moieties which are members of a binding pair, the lack of guidance and examples in the specification showing which ApoB proteins can be used and which heterologous moieties can be fused to said truncated ApoB proteins, and the unpredictability in the art with regards to the effects of fusing various peptides, one of ordinary skill in the art would require further, undue experimentation in order to make and use any lipoprotein compound delivery particle comprising

any ApoB other than ApoB 17, wherein said ApoB is fused to any other moiety other than a single chain antibody.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 93-114 rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a lipoprotein compound delivery particle comprising a truncated ApoB protein. The claims do not require the truncated ApoB protein of the instant invention to have any biological activity, nor any particular structure other than having a deleted LDL receptor binding region. The specification lists numerous potential truncated ApoB polypeptides; however, only one truncated ApoB polypeptide, ApoB 17, is described as having the ability to sequester lipids and delivery pharmaceutical agents. Given the broadest reasonable interpretation, a truncated ApoB protein can be represented by the ApoB proteins listed on page 13 of the specification, or any fragment, regardless of size, of ApoB. The specification does not describe any small fragments of ApoB, or any other truncated ApoB protein from those listed on page 13 that are capable of sequestering lipids and acting as a drug delivery vehicle. Thus, the specification has not adequately described the genus of truncated ApoB proteins that would be expected to be useful in the claimed invention.

The claims are also drawn to a genus of fused heterologous moieties, which are fused to the truncated ApoB protein. Although the specification describes antibodies, including single chain antibodies, as fused heterologous moieties that can be fused to said truncated ApoB protein, there is no description of any other fused heterologous moiety that can be used in the claimed manner. There are not functional limitations for said fused heterologous moiety in the claims, and no structural limitations other than being a member of a specific binding pair, or being a protein. The specification describes an anti-HER2 antibody fused to ApoB 17, but does not describe any other fused heterologous moiety. Furthermore, the specification does not describe which truncated ApoB/fused heterologous moiety combinations would still be capable of (a) sequestering lipid, and (b) retain the biological function of the heterologous moiety. Therefore, the claims are also drawn to a genus of fused heterologous moieties that have not been adequately described in the specification

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors

to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a requirement that the claimed lipoprotein compound delivery particle comprise any polypeptide that could be considered a truncated ApoB protein, and further comprise any "fused heterologous moiety". There is no identification of any particular portion of a truncated ApoB protein, or any portion of a fused heterologous moiety, that must be conserved in order to maintain function. Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 93-114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claim 93 recites the acronym LDL, which is not defined by the claim and thus renders the claim indefinite. Acronyms should be defined upon the first use in a claim. Claims 94-114 are rejected for depending from a rejected base claim.

2. Claims 93-114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claim 93 recites a lipoprotein compound delivery particle comprising a truncated ApoB protein, "said particle having a deleted LDL receptor binding region." It is not clear if the claimed delivery particle has a deleted LDL receptor binding region, of if said truncated ApoB protein has a deleted LDL receptor binding region. For the purpose of examination, the claim has been interpreted as comprising a truncated ApoB protein, wherein said truncated ApoB protein has a deleted receptor binding region. Furthermore, the term "having" can be interpreted in terms of possessing something. For example, the claim can be interpreted as a truncated ApoB protein (or delivery particle) *comprising* a deleted LDL receptor region. It is not clear how a truncated ApoB can comprise a deleted region. In other words, if the region has been deleted, how can the truncated ApoB (or delivery particle) "have" the LDL receptor region?

3. Claim 101 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites an ApoB selected from "the group consisting of through apoB74". The claim does not recite a lower limit for the claimed range, and thus is indefinite with regards to the claimed group of ApoB proteins.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 93-96, 99-107, and 109-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Protter *et al* (WO 87/02061). The claims of the instant invention are drawn to a lipoprotein compound delivery particle comprising various percentages of a lipophilic compound to be delivered, at least one polar lipid, at least one neutral lipid, and a truncated ApoB protein having a deleted receptor binding region. The claims are further drawn to said ApoB protein fused to a heterologous moiety, including peptides and specifically antibodies. The claims also recite mature ApoB, mammalian ApoB, and specifically human ApoB, and truncated ApoB proteins up to ApoB 74. The claims recite polar lipids, including phosphatidylcholine, and neutral lipids, including triglyceride.

Protter *et al* teaches compounds for delivery of therapeutic agents, wherein said compounds comprise human ApoB 26, or sub-fragments thereof (see claim 2; see Fig 2. for human ApoB). ApoB 26 is disclosed by Protter *et al* to be a fragment of the mature ApoB 100 protein (p. 4, lines 6-16). Protter *et al* also teaches that various target peptides can be fused to ApoB, including immunoglobulins (see claims 5-6), and also discloses a number of active compounds that can be delivered (see p. 12-13). Furthermore, Protter *et al* discloses that the ApoB compound can further comprise a lipid emulsion (see claim 7), and teaches emulsion of said ApoB compound in Intralipid™, which comprises phospholipids such as phosphatidylcholine and triglycerides (see p. 25, line 29 – p. 26, line 11). Therefore, Protter *et al* discloses a compound comprising a truncated ApoB protein (ApoB 26 or sub-fragments thereof), an

active compound to be delivered, and polar (phospholipids) and neutral (triglyceride) lipids. Protter *et al* also discloses that lipoprotein delivery of various biological agents is advantageous when the compound to be delivered is associated with toxicity to host cells (see p. 1-2). However, Protter *et al* is silent regarding any specific concentrations of ApoB, compound to be delivered, or specific concentrations of polar and neutral lipids.

However, one of ordinary skill in the art, at the time the instant invention was conceived, would have been motivated to follow the teachings of Protter *et al* and create a lipoprotein particle that meets the limitations of the instant claims. The motivation to do so comes from the disclosure of Protter *et al*, which teaches a lipoprotein compound delivery particle comprising truncated ApoB (specifically ApoB 26), wherein said delivery particle can further comprise an additional therapeutic agent for delivery, and wherein said ApoB can be fused to another moiety, including antibodies. Protter *et al* also provides motivation by teaching that the disclosed lipoprotein delivery compound is useful for overcoming toxicity/side-effects of therapeutic agents delivered by other methods.

Furthermore, although Protter *et al* does not specifically recite percentages of ApoB, polar lipid, neutral lipid, and agent to be delivered, such as recited in claims 93, 109, 111, and 113, it is noted that one of ordinary skill in the art would be motivated to optimize the formulation of Protter *et al*, and could therefore arrive at the claimed percentages by routine optimization. MPEP 2144.05 states:

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223, 235, (CCPA 1955).

In the instant case, the general conditions of the claims, namely a compound comprising a truncated ApoB protein, an agent to be delivered, and both polar and neutral lipids, is disclosed by Protter *et al*. It is also noted that although discoidal, small emulsion particles, and large emulsion particles are not explicitly taught by Protter *et al*, compounds meeting the limitations of claims 93, 109, 111, and 113, obtained via routine optimization of Protter *et al*, would be expected to inherently be discoidal, small emulsion, or large emulsion particles, respectively, because the specification teaches that the formulations set forth in claims 93, 109, 111, and 113 produce discoidal, small emusion particles, or large emulsion particles, respectively.

Finally, although Protter *et al* does not specifically teach particles with specific diameters, it is noted that the compound of Protter *et al*, by virtue of comprising a truncated ApoB protein, compound for delivery, and a polar and neutral lipid, would be expected to have a diameter of less than 18 nanometers, or between 5 and 5000 nanometers, because the composition is the same as that of the instant invention.

Because the USPTO does not have the facilities for testing the compound of Protter *et al*, the burden is on the applicant to show a novel and unobvious difference between the claimed compound and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

2. Claims 97-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Protter *et al* (WO 87/02061), in view of Park *et al* (*Cancer Letters*, 1997, 118: 153-160). Claims 97-98 are drawn to the lipoprotein compound delivery particle discussed above, wherein the truncated apoB protein further comprises a single chain antibody, and specifically, a single chain anti-HER2 antibody. The disclosure of Protter *et al* is discussed *supra*. Protter *et al* is silent regarding incorporation of a single chain antibody, and is also silent regarding anti-HER2 antibodies.

Park *et al* shows administration of anti-HER2 antibodies in liposomes, and teaches that such administration is advantageous because it improves the effectiveness of anti-HER2 antibodies because it reduces toxicity against non-cancer cells (see abstract; p. 159, 1st full paragraph). Specifically, Park *et al* teaches administration of anti-HER2 Fab fragments, which can be considered to be a single chain antibody because they comprise only the Fab region. Park *et al* is silent regarding administration of anti-HER2 antibodies in liposomes comprising ApoB, or fusion of anti-HER2 antibodies to ApoB.

Therefore, one of ordinary skill in the art, at the time the instant invention was filed, would have been motivated to create a lipoprotein compound delivery particle comprised of a truncated ApoB protein, wherein said ApoB protein further comprises a single chain anti-HER2 antibody. The skilled artisan would be motivated to do so because Park *et al* teaches that anti-HER2 antibodies are effectively delivered by liposomes and that formulation in liposomes reduces antibody clearance and enhances tumor accumulation of antibodies (p. 154, 1st column)., and thus Park *et al* provides motivation to incorporate a single chain anti-HER2 antibody into the lipoprotein compound of Protter *et al*.

3. Claim 108 is rejected under 35 U.S.C. 103(a) as being unpatentable over Protter *et al* (WO 87/02061), in view of Sharma *et al* (*Int. J. Cancer*, 1997, 71:103-107). Claim 108 is further drawn to the claimed lipoprotein compound delivery particle comprising paclitaxel as the compound to be delivered. The teachings of Protter *et al* are discussed *supra*. Protter *et al*, however, is silent with regards to paclitaxel.

One of ordinary skill in the art, at the time the instant invention was filed, would have been motivated to incorporate paclitaxel as the compound to be delivered by the particle disclosed in Protter *et*

al because the disclosed lipoprotein particle can target therapeutic agents to target tissues or the liver for intermediate processing (Protter *et al*, p. 2, 1st paragraph), and because formulation of paclitaxel in liposomes of this type are less toxic than convention Cremophor/ethanol formulations, as discussed in Sharma *et al*. Thus, based on the disclosures of Protter *et al* and Sharma *et al*, it would be obvious to one of ordinary skill in the art to create a lipoprotein compound delivery particle comprising ApoB 26, or fragments thereof, a neutral lipid, a polar lipid, and paclitaxel.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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